



American
National
Standard

ANSI/AAMI/ISO 13408-1:2023

Aseptic processing of health care products—
Part 1: General requirements

Aseptic processing of health care products—Part 1: General requirements

Approved 23 January 2024 by
AAMI

Approved 07 May 2024 by
American National Standards Institute

Abstract: This document specifies the general requirements for, and offers guidance on, processes, programs and procedures for development, validation and routine control of aseptic processing of health care products. This document includes requirements and guidance relative to the overall topic of aseptic processing.

Keywords: aseptic processing, health care products, general requirements

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Published by

AAMI
901 N. Glebe Road, Suite 300
Arlington, VA 22203

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Printed in the United States of America

ISBN 978-1-57020-898-0

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Committee representation

Association for the Advancement of Medical Instrumentation

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The adoption of ISO 13408-1:2023, *Aseptic processing of health care products — Part 1: General requirements* as an American National Standard was initiated by the AAMI ST-WG09, Aseptic Processing Working Group. AAMI ST-WG09 provides input to the AAMI Sterilization Committee which is the responsible group for providing the U.S. input to the relevant group in ISO/TC 198. U.S. representatives from AAMI ST-WG09 and the TAG played an active part in developing the ISO document.

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Background of ANSI/AAMI adoption of ISO 13408-1:2023

As indicated in the foreword to the main body of this document (page ix), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO/TC 198, Sterilization of health care products to cancel and replace a second edition (ISO 13408-1:2008) which has been technically revised. It also incorporates ISO 13408-1:2008/Amd 1:2013.

U.S. participation in ISO/TC 198 is organized through the U.S. Technical Advisory Group, AAMI Sterilization Committee, administered by the Association for the Advancement of Medical Instrumentation. Experts from the United States made a considerable contribution to this standard.

AAMI encourages its committees to harmonize their work with International Standards in the area of aseptic processing. Upon review of ISO 13408-1:2023, the AAMI Sterilization Committee and the AAMI Aseptic Processing Working Group decided to adopt it verbatim, as a revision of ANSI/AAMI/ISO 13408-1:2008/(R)2017 & A1:2013.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication.

As used within the context of this document, “shall” indicates requirements strictly to be followed to conform to the recommended practice. “Should” indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but is not prohibited.

“May” is used to indicate that a course of action is permissible within the limits of the standard. “Can” is used as a statement of possibility and capability. Finally, “must” is used only to describe “unavoidable” situations, including those mandated by government regulation.

NOTE Users of this standard are advised that this document is an AAMI identical adoption of an ISO document and that the following international conventions have been carried over to the AAMI publication:

- British English spelling (e.g. colour instead of color)
- Use of SI units (e.g. metres instead of feet, Celsius instead of Fahrenheit, etc.)
- Decimal comma instead of a decimal point (e.g. 1 000,15 instead of 1,000.15)

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 901 N. Glebe Road, Suite 300, Arlington, VA 22203.

NOTE—Beginning with the ISO foreword on page ix, this American National Standard is identical to ISO 13408-1:2023.

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 204, *Sterilization of medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This third edition cancels and replaces the second edition (ISO 13408-1:2008) which has been technically revised. It also incorporates ISO 13408-1:2008/Amd 1: 2013.

The main changes are as follows:

- a complete restructuring of the document;
- inclusion of a diagram to explain the relationship between the ISO 13408 series and ISO 18362;
- revision of the normative references;
- alignment of definitions with ISO 11139:2018;
- positioning of the document to recognize current and future advances in sterile manufacturing technology, acknowledging that new approaches to aseptic processing are transforming classical aseptic processing;
- promotion of aseptic processing principles and the systematic implementation of quality risk management (QRM), including for aseptic process design, and microbiological contamination and particulate contamination control;
- provision of guidance for different types of aseptic processing, for example, manual processing systems to automated robotic processing systems;

- deletion of tables from the previous edition of this document referring to acceptance criteria for process simulation (media fill) qualification and requalification;
- encouraging adoption of advanced aseptic processing technologies and continuous process improvement to improve assurance of sterility;
- recognition that alternative or rapid microbiological methods (RMMs) provide timely microbiological data vital for process monitoring and control, and for product release;
- inclusion of a series of informative annexes providing guidance on defining an aseptic process, including risks to be considered, aseptic processing areas (APAs), classification of cleanrooms, aseptic process flow, closed systems and robotics, and qualification of a cleanroom clothing system.

A list of all parts in the ISO 13408 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Wherever possible, health care products intended to be sterile should be terminally sterilized in their final sealed container by a terminal sterilization process, which has been validated to achieve a specified sterility assurance level (SAL). ISO/TC 198 has developed standards for terminal sterilization of health care products, for example (but not restricted to): the ISO 11137 series (radiation sterilization), ISO 17665-1 (moist heat sterilization), ISO 20857 (dry heat sterilization), ISO 11135 (ethylene oxide sterilization) and ISO 14160 (liquid chemical sterilization).

Where a health care product is intended to be sterile and cannot withstand terminal sterilization in its final container, aseptic processing provides an acceptable alternative for product manufacture.

ISO/TC 198 also developed ISO/TS 19930, which provides guidance on aspects of a risk-based approach to assuring sterility of terminally sterilized, single-use health care product that is unable to withstand processing to achieve maximally a 10^{-6} SAL.

Aseptic processing produces a sterile product in its final container by the assembly of component parts (e.g. product, container and container closure) that have been sterilized separately by validated and controlled processes suitable for each component part. Each of these assembly processes can introduce error that can result in product contamination. Furthermore, contamination can be introduced from the personnel, equipment or environment when the sterilized components are brought together to create the final product. It is important to control all possible sources of contamination so that the aseptic manufacturing process maintains sterility of previously-sterilized components during product filling or assembly, and sealing. Fundamentally, aseptic processing minimises the probability of a chance event of microbial contamination occurring. The rationale to use aseptic processing is product dependent and is not based solely on manufacturing considerations.

Examples of applications in which aseptic processing is used include:

- aseptic handling and filling of solutions, suspensions, semisolids and powders;
- aseptic handling, transfer and packaging of solid products including solid medical devices;
- aseptic handling, transfer and packaging of combination products;
- aseptic handling of tissues or biological production systems (e.g. vaccines).

Sterilization processes for product and components used as a prerequisite for aseptic processing are established and validated separately to aseptic processing activities.

Traditionally, aseptic processing has been carried out in cleanrooms and associated controlled environments to provide an environment in which the air supply, materials, equipment and operators are regulated to maintain sterility of previously-sterilized components. Advances in aseptic processing include systems that prevent the direct intervention of operators with open-product containers or exposed-product contact surfaces in the critical processing zone, for example, the use of fully enclosed barrier systems (e.g. isolators), automation and robotics. This can mean that a traditional cleanroom is not always appropriate for aseptic processing activities.

To provide assurance of sterility for an aseptically processed product, this document identifies three key activities in the development and operation of an aseptic process to reduce and control particulate and microbial contamination risks:

- process design;
- risk assessment;
- contamination control strategy (CCS).

An effective risk management approach is an essential tool for the development, validation and control of aseptic processing. Only when risks of particulate and microbiological contamination have been identified, and where possible eliminated, or minimized and controlled, can an aseptic process be considered suitable for its intended purpose.

Controls for some infectious agents, e.g. protozoa or parasites, can require a multifaceted approach to assure component or product safety. These types of infectious agents are not considered in the ISO/TC 198 standards for terminal sterilization or aseptic processing. Guidance can be found in ISO 18362 applicable good manufacturing practice (GMP) regulations and the EDQM guide^[28].

This document describes the fundamental requirements of aseptic processing regardless of the nature of the aseptic process, e.g. small-scale versus large-scale, open- versus closed-processing, single-use, disposable sterile systems, traditional cleanroom versus isolator systems, manual versus automated or robotic systems, autologous sterile products, processes with post-aseptic lethal treatments and processes using real-time microbiological monitoring. It does not, however, describe the requirements for other manufacturing processes upstream or downstream of aseptic processing activities. This document acknowledges the different geographical regulatory approaches to aseptic processing and recognizes that new approaches to aseptic processing are transforming classical aseptic processing. It recognizes that future improvements in aseptic processing rely on improved use of technology for both existing and new products, for example, sterile advanced therapy medicinal products.

To encourage adoption of suitable, advanced aseptic processing technologies and continuous process monitoring, this document introduces the concept of recognising efforts in risk-based process design, particulate and microbiological contamination control and risk management, to justify consideration of alternative approaches to demonstrating ongoing process effectiveness, for instance reduced frequency of requalification, sampling, or for real-time release of finished product.

Assurance of sterility for an aseptically processed product should not be confused with the term, 'sterility assurance level (SAL)'. SAL is a mathematical extrapolation applicable only to a validated and controlled terminal sterilization process of known microbial lethality and which is delivered to each individual sealed unit of product subject to that process. Due to the variability and chance nature of occurrence of microbial contamination during aseptic processing, aseptic process simulation (APS) does not result in a mathematical probability of there being a single, viable microorganism in a contaminated unit, but rather results in an indication of what can happen in the routine processing of subsequent product batches (see ISO/TS 19930:2017, Clause 4).

This document specifies the requirements for general aspects of aseptic processing of health care products. Requirements and guidance for other processes often employed during aseptic processing are specified in ISO 13408-2 to ISO 13408-7, i.e. sterilizing filtration (ISO 13408-2), lyophilization (ISO 13408-3), clean-in-place (CIP) technologies (ISO 13408-4), sterilization in place (SIP) (ISO 13408-5), isolator systems (ISO 13408-6) and alternative processes for medical devices and combination products (ISO 13408-7).

ISO 18362 specifies the minimum requirements for, and provides guidance on, a risk-based approach for the processing of cell-based health care products (CBHPs) requiring control of viable and non-viable microbial contamination. It is applicable to CBHPs labelled 'sterile', as well as to those that are not labelled 'sterile'. For aseptic processing of CBHPs to be labelled sterile, ISO 18362 refers normatively to this document and ISO 13408-7. A CBHP that incorporates non-sterile starting material cannot meet the ISO 11139 definition of aseptic processing, which amongst other things, requires the use of sterile product and components. ISO 18362, therefore also includes requirements and guidance for the processing of such products to reduce and control microbial contamination risks.

The relationship between the ISO 13408 series and ISO 18362 is shown in [Figure 1](#).

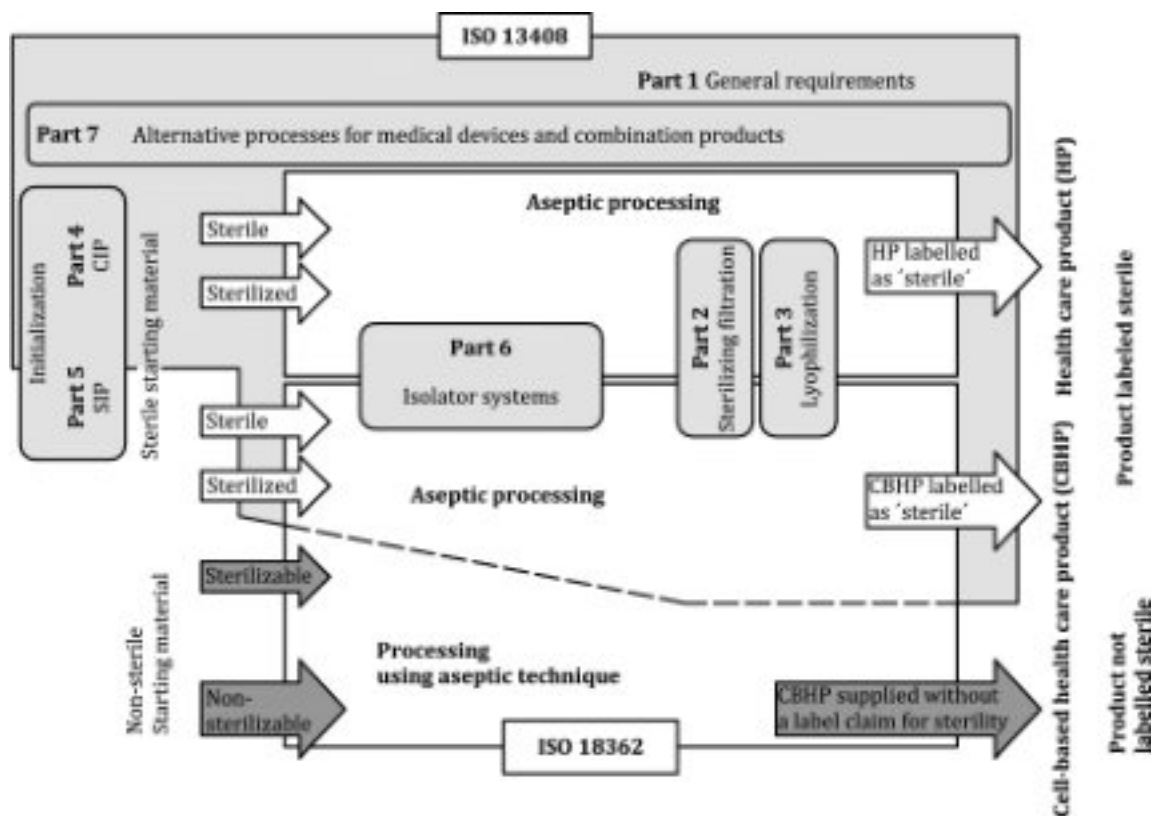


Figure 1 — Relationship between the ISO 13408 series and ISO 18362

Aseptic processing of health care products—Part 1: General requirements

1 Scope

This document specifies the general requirements for, and offers guidance on, processes, programs and procedures for development, validation and routine control of aseptic processing of health care products.

This document includes requirements and guidance relative to the overall topic of aseptic processing.

Specific requirements and guidance on various specialized processes and methods related to sterilizing filtration, lyophilization, clean-in place (CIP) technologies, sterilization in place (SIP) and isolator systems are given in the other parts of the ISO 13408 series.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 13408-2, *Aseptic processing of health care products — Part 2: Sterilizing filtration*

ISO 13408-6, *Aseptic processing of health care products — Part 6: Isolator systems*

ISO 14644-1:2015, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration*

ISO 14644-2, *Cleanrooms and associated controlled environments — Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration*

ISO 14644-4, *Cleanrooms and associated controlled environments — Part 4: Design, construction and start-up*

ISO 14644-7, *Cleanrooms and associated controlled environments — Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

- ISO Online browsing platform: available at <https://www.iso.org/obp>
- IEC Electropedia: available at <https://www.electropedia.org/>

3.1

action level

value from monitoring that necessitates immediate intervention

[SOURCE: ISO 11139:2018, 3.5]

3.2

advanced aseptic processing

aseptic processing (3.5) where direct intervention by personnel wearing cleanroom garments with open product containers or exposed product contact surfaces, in the critical processing zone, is not necessary or is not allowed

3.3

airlock

enclosure with interlocked doors designed to maintain pressure control between adjacent areas

[SOURCE: ISO 11139:2018, 3.10]

3.4

alert level

value from monitoring providing early warning of deviation from specified conditions

[SOURCE: ISO 11139:2018, 3.11]

3.5

aseptic processing

handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials, equipment and personnel are regulated to maintain sterility

[SOURCE: ISO 11139:2018, 3.14]

3.6

aseptic processing area

APA

facilities for *aseptic processing* (3.5), consisting of several zones

[SOURCE: ISO 11139:2018, 3.15]

3.7

bioburden

population of viable microorganisms on or in a product and/or sterile barrier system

Note 1 to entry: For the purposes of aseptic processing, the bioburden of concern is that on or in the product including all factors affecting it such as raw materials, intermediates, other components and equipment.

[SOURCE: ISO 11139:2018, 3.23, modified – Note 1 to entry added.]

3.8

bio-decontamination

removal and/or reduction of biological contaminants to an acceptable level

[SOURCE: ISO 11139:2018, 3.27]

3.9

cleaning

removal of contaminants to the extent necessary for further processing or for intended use

[SOURCE: ISO 11139:2018, 3.46]

3.10

cleanroom clothing system

combination of reusable or single-use cleanroom garments and other accessories (e.g. undergarments, footwear, socks, head coverings, face masks, eye coverings, gloves) designed to minimize the risk of contamination during activities performed in *aseptic processing area (APA)* ([3.6](#))

Note 1 to entry: The cleanroom clothing system can also protect personnel against other hazards (e.g. chemical, biological) depending on the products handled in the aseptic environment.

3.11

closed system

<*aseptic processing*> ([3.5](#)) means to prevent egress of hazardous agents and ingress of extrinsic contamination

[SOURCE: ISO 11139:2018, 3.50]

3.12

combination product

entity presented as a single health care product that physically, chemically, or otherwise brings together or mixes items regulated under separate legislation

Note 1 to entry: The entity could be a combination of medical device and medicinal product or biopharmaceutical product.

[SOURCE: ISO 11139:2018, 3.54]

3.13

correction

action to eliminate a detected nonconformity

Note 1 to entry: A correction can be made in advance of, in conjunction with or after a *corrective action* ([3.14](#)).

Note 2 to entry: A correction can be, for example, rework or regrade.

[SOURCE: ISO 9000:2015, 3.12.3]

3.14

corrective action

action to eliminate the cause of a nonconformity and to prevent recurrence

Note 1 to entry: There can be more than one cause for a nonconformity.

Note 2 to entry: *Corrective action* ([3.14](#)) is taken to prevent recurrence whereas *preventive action* ([3.32](#)) is taken to prevent occurrence.

Note 3 to entry: This constitutes one of the common terms and core definitions for ISO management system standards given in Annex SL of the Consolidated ISO Supplement to the ISO/IEC Directives, Part 1. The original definition has been modified by adding Notes 1 and 2 to entry.

[SOURCE: ISO 9000:2015, 3.12.2]

3.15

critical control point

point, step or procedure of an aseptic process at which control can be applied and is essential to prevent or eliminate a hazard or reduce it to an acceptable level

[SOURCE: ISO 5667-13:2011, 3.3, modified — Added "of an aseptic process" to the definition.]

3.16

critical processing zone

location within the aseptic processing area in which product and critical surfaces are exposed to the environment

[SOURCE: ISO 11139:2018, 3.67]

3.17

critical surface

surface that might come into direct contact with a product, including its containers or closures, posing a risk of contamination

[SOURCE: ISO 11139:2018, 3.68]

3.18

depyrogenation

process used to remove or deactivate pyrogenic substances to a specified level

Note 1 to entry: Pyrogenic substances include bacterial *endotoxins* ([3.23](#)).

[SOURCE: ISO 11139:2018, 3.77]

3.19

design qualification

process for verification that the proposed specification for the facility, equipment or system meets the expectation for the intended use

[SOURCE: ISO 11139:2018, 3.220.1]

3.20

direct support zone

protective area directly surrounding a critical processing zone

[SOURCE: ISO 11139:2018, 3.81]

3.21

disinfectant

chemical or combination of chemicals used for disinfection

[SOURCE: ISO 11139:2018, 3.82]

3.22

disinfection

process to inactivate viable microorganisms to a level previously specified as being appropriate for a defined purpose

Note 1 to entry: Level could be a log reduction or an absolute value.

[SOURCE: ISO 11139:2018, 3.84, modified — Added Note 1 to entry.]

3.23

endotoxin

lipopolysaccharide component of the cell wall of Gram-negative bacteria that is heat stable and elicits a variety of inflammatory responses in animals and humans

[SOURCE: ISO 11139:2018, 3.101]

3.24

gowning procedure

specified actions for putting on protective garments in a manner commensurate with the cleanliness level of the room

[SOURCE: ISO 11139:2018, 3.127]

3.25

health care product

medical device, including in vitro diagnostic medical device, or medicinal product, including biopharmaceutical

[SOURCE: ISO 11139:2018, 3.132]

3.26

indirect support zone

location within the aseptic processing area that protects the direct support zone

Note 1 to entry: The required grade of cleanliness of the indirect support zone depends on the aseptic processing technologies and activities performed.

[SOURCE: ISO 11139:2018, 3.142]

3.27

installation qualification

IQ

process of establishing by objective evidence that all key aspects of the process equipment and ancillary system installation comply with the approved specification

[SOURCE: ISO 11139:2018, 3.220.2]

3.28

isolator

<aseptic processing> (3.5) enclosure capable of preventing ingress of contaminants by means of physical separation of the interior from the exterior that is capable of being subject to reproducible interior bio-decontamination and where operators always remain separated from the interior of the enclosure by means of an absolute physical barrier

Note 1 to entry: If containment requirements apply (i.e. aseptic processing of hazardous materials) egress also has to be prevented.

[SOURCE: ISO 11139:2018, 3.149, modified — Note 1 to entry added.]

3.29

operational qualification

OQ

process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO 11139:2018, 3.220.3]

3.30

packaging system

combination of a sterile barrier system and protective packaging

[SOURCE: ISO 11139:2018, 3.192]

3.31

performance qualification

PQ

process of establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements

[SOURCE: ISO 11139:2018, 3.220.4]

3.32

preventive action

action to eliminate the cause of a potential nonconformity or other potential undesirable situation

Note 1 to entry: There can be more than one cause for a potential nonconformity.

Note 2 to entry: Preventive action is taken to prevent occurrence whereas *corrective action* ([3.14](#)) is taken to prevent recurrence.

[SOURCE: ISO 9000:2015, 3.12.1]

3.33

process analytical technology

PAT

system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

[SOURCE: ICH Q8, 3]

3.34

process simulation

exercise that mimics the manufacturing process or portions of the process in order to demonstrate the capability of that process

[SOURCE: ISO 11139:2018, 3.212]

3.35

protective packaging

configuration of materials designed to prevent damage to the sterile barrier system and its contents from the time of their assembly until the point of use

[SOURCE: ISO 11139:2018, 3.219]

3.36

qualification

activities undertaken to demonstrate that utilities, equipment, and methods or modes are suitable for their intended use and perform properly

Note 1 to entry: Qualification of equipment and/or processes generally includes *installation qualification* ([3.27](#)), *operational qualification* ([3.29](#)) and *performance qualification* ([3.31](#)).

[SOURCE: ISO 11139:2018, 3.220]

3.37

quality by design

QbD

systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

[SOURCE: ICH Q8, 4]

3.38

restricted access barrier system

RABS

system that provides a segregated, but not sealed, controlled environment using physical barriers and air overspill and which is capable of being subject to reproducible interior bio-decontamination

Note 1 to entry: Operators are separated from the controlled environment using an absolute physical barrier, but can access the controlled environment by opening the physical barrier (e.g. a door).

3.39

risk assessment

overall process comprising a risk analysis and a risk evaluation

[SOURCE: ISO/IEC Guide 51:2014, 3.11]

3.40

risk control

process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

[SOURCE: ISO/IEC Guide 63:2019, 3.12]

3.41

risk evaluation

process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

[SOURCE: ISO/IEC Guide 63:2019, 3.14]

3.42

risk management

systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[SOURCE: ISO/IEC Guide 63:2019, 3.15]

3.43

separative device

equipment utilizing constructional and dynamic means to create assured levels of separation between the inside and outside of a defined volume

Note 1 to entry: Some industry-specific examples of separative devices are clean air hoods, containment enclosures, glove boxes, isolators and mini-environments.

[SOURCE: ISO 11139:2018, 3.250]

3.44

shift

scheduled period of work or production staffed by a single defined group of workers

[SOURCE: ISO 11139:2018, 3.253]

3.45

sterile

free from viable microorganisms

[SOURCE: ISO 11139:2018, 3.271]

3.46

sterile barrier system

SBS

minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the sterile contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.47

sterilization

validated process used to render a product free from viable microorganisms

Note 1 to entry: In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

Note 2 to entry: Note 1 to entry is not applicable to sterilizing filtration.

[SOURCE: ISO 11139:2018, 3.277, modified — Note 2 to entry added.]

3.48

terminal sterilization

process whereby a product is sterilized within its sterile barrier system

[SOURCE: ISO 11139:2018, 3.295]

3.49

unidirectional airflow

air stream which has a defined direction

[SOURCE: ISO 11139:2018, 3.308]

3.50

unit operation

defined part of a manufacturing process

Note 1 to entry: See example of a flowchart in [Annex E](#).

[SOURCE: ISO 11139:2018, 3.309, modified — Note 1 to entry added.]

3.51

validation

confirmation process, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

[SOURCE: ISO 11139:2018, 3.313, modified — Notes to entry deleted.]

4 General

4.1 Aseptic processing activities are undertaken in accordance with quality risk management (QRM) principles to manage microbiological contamination risks to product quality. To ensure the consistent implementation of the requirements specified in this document, the necessary processes shall be established, implemented and maintained. Processes of particular importance in relation to aseptic processing include, but are not limited to:

- control of documentation, including records,
- assignment of management responsibility,
- provision of adequate resources, including competent human resources and infrastructure,
- control of the product provided by external parties,
- judicious decision-making during product lifecycle, including modernizing and improving aseptic processes to further reduce risks to product quality,
- establishment of aseptic processing and maintenance of a state of microbiological control,
- investment in aseptic process understanding and monitoring of process performance,
- identification and traceability of the product throughout the process, and
- control of a non-conforming product including related corrective and preventive actions.

NOTE Quality management is a management function that directs and controls an organisation in relation to quality. The essential concepts of good manufacturing practice (GMP), quality control and quality assurance are interconnected within the context of quality management. Their significance in aseptic processing of medicines and CBHPs is described in national and regional codes of GMP. For medical devices, ISO 13485 covers all stages of the product lifecycle in the context of quality management systems for regulatory purposes. National and/or regional regulatory requirements for the provision of health care products can require the implementation of a full quality management system and the assessment of that system by a recognized conformity assessment body.

4.2 A process shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this document.

5 Principles of aseptic processing

5.1 General

5.1.1 Aseptic processing is an activity composed of individual unit operations that shall be effectively combined to maintain sterility. These operations shall be documented and justified.

5.1.2 The use of advanced aseptic processing systems shall be considered as part of the risk management process.

NOTE 1 The aseptic processing encompasses all set-up activities conducted in the aseptic processing area (APA) in preparation for product manufacture and all production steps following sterilization of product and components until sealing of the final container or package.

NOTE 2 Further guidance on unit operations and typical elements of aseptic processes can be found in [Annex A](#).

5.1.3 At each stage of the design, development qualification and operation of aseptic processing, risks shall be assessed, controlled and where appropriate, monitored. Risk assessments shall be documented.

5.1.4 A contamination control strategy (CCS) shall be developed, which describes how the identified risks are monitored and controlled to minimise the risk of product contamination.

5.1.5 The effectiveness of risk control measures shall be assessed.

5.1.6 A risk-based approach shall be used in the design of processes, layouts, activities and testing regimes.

[Figure 2](#) illustrates the activities that are key to development and operation of aseptic processing.



Figure 2 — Key activities in the development and operation of an aseptic process and their relationships

5.2 Use of an aseptic process

The requirement for a product to be supplied sterile shall be identified as an input to process design and development.

The ability of the product to withstand a terminal sterilization process that delivers a specified sterility assurance level (SAL) shall be assessed.

Where possible, a sterile product shall be sterilized in its final container by a validated terminal sterilization process. If a product is not able to withstand the processing conditions for terminal sterilization, then aseptic processing provides an acceptable alternative for manufacture of sterile product.

The rationale for selection of aseptic processing for a product shall be documented. The rationale shall include the strategies investigated to overcome the detrimental effects on a product of a terminal sterilization process and technical reasons to support the selection of aseptic processing for that product. The rationale shall include, but is not limited to, discussion of:

- a) The feasibility of changing materials or formulation to enable the product to withstand the processing conditions for a terminal sterilization process.

- b) The feasibility of redesigning or modifying the product or sterile barrier system (SBS) to enable the product to withstand the processing conditions for terminal sterilization.
- c) The feasibility of changing the presentation of the product to a sterilization process to reduce the extent of processing conditions for terminal sterilization.
- d) The feasibility of reducing and controlling the product and packaging bioburden to allow the use of sterilizing conditions that have a less detrimental effect.
- e) The feasibility of changing the process parameters of a sterilization process to reduce detrimental effects on the product.
- f) The feasibility of establishing a terminal sterilization process with less severe processing conditions than an overkill process, e.g. use of the bioburden-based, or combined bioburden-biological indicator approaches to the process definition.
- g) The feasibility of considering different terminal sterilization modalities to mitigate detrimental effects associated with a particular terminal sterilization modality.
- h) Where applicable, evidence that product packaging, which cannot be terminally sterilized, provides enhanced application and/or therapeutic advantages.
- i) For a product with a short shelf-life, whether terminal sterilization adversely affects product stability and further reduces shelf-life.
- j) Where applicable, the volume administered per dose, noting that where possible, a large volume parenteral product shall be terminally sterilized.
- k) A comprehensive evaluation of the benefit-risk ratio in relation to aseptic processing versus terminal sterilization.

The rationale to select aseptic processing shall still be documented when a product:

- contains a material or substance that is clearly recognized as incompatible with terminal sterilization; or
- is recognized as being manufactured traditionally by aseptic processing, for example, some ophthalmic preparations,

NOTE 1 Guidance can be found in ISO/TS 19930:2017, Clause 7, Reference [35] and Reference [46].

NOTE 2 National or regional requirements can apply to aseptically processed medical devices that are designated 'sterile', for example, EN 556-2 and ANSI/AAMI ST67:2019.

5.3 Core elements

Core elements that shall be considered during the process design, CCS and risk assessment are:

- a) environment and air handling (including facility and premises);
- b) materials and components (including surfaces);
- c) handling and processing (including personnel);
- d) equipment (e.g. barrier systems, filling and sealing equipment, automation, robotics) and utilities;
- e) the product;

- f) flow management;
- g) cleaning and disinfection.

NOTE There can be other elements to consider depending on either the product or the process, or both.

5.4 Aseptic processing zones

5.4.1 General

Aseptic processing zones shall be specified for the aseptic processing activities.

NOTE 1 Further guidance on aseptic processing zones is given in [Annex C](#).

NOTE 2 Further guidance on classification of cleanrooms is given in [Annex D](#).

5.4.2 Critical processing zone

The critical processing zone shall be segregated and operated in a way that ISO 14644-1:2015, Class 5 conditions are maintained.

NOTE 1 This document refers to the classifications of air cleanliness by particle concentration according to ISO 14644-1, which are referred to as, for example, ISO Class 5, ISO Class 8 etc.

NOTE 2 Examples of activities performed in a critical processing zone can include:

- a) aseptic assembly of filling equipment;
- b) aseptic connections;
- c) aseptic compounding and mixing;
- d) staging and conveying of sterilized primary packaging materials;
- e) aseptic filling, stoppering, transfer of open or partially stoppered containers, including interventions;
- f) environmental monitoring.

Where separative devices are used for segregation of critical processing zones, either ISO 13408-6 or ISO 14644-7, or both shall apply.

5.4.3 Direct support zones

For a critical processing zone, a direct support zone with at least an ISO 14644-1:2015, ISO Class 7 environment shall be provided to prevent contamination of the critical processing zone.

In the case of an isolator system or similar separative device, the necessary surrounding environmental class shall be determined according to ISO 13408-6.

NOTE Examples of activities usually performed in the direct support zones include:

- a) transport and preparation of packaged materials for introduction into the critical processing zone;
- b) preparation of operators for interventions in the critical processing zone (e.g. disinfection of gloves, staging of tools).

5.4.4 Indirect support zones

Indirect support zones within the APA shall be segregated from direct support zones. The required grade of cleanliness depends on the separation mechanism chosen.

NOTE 1 A clean zone corresponding to ISO 14644-1:2015, ISO Class 8 is usually provided.

NOTE 2 Examples of activities usually performed in an indirect support zone include:

- a) preparation of product solutions to be filtered;
- b) assembly of cleaned equipment to be sterilized;
- c) cleaning of equipment.

6 Process design, development and risk management

6.1 General

6.1.1 The inputs, including product attributes, for designing the aseptic process shall be documented.

A formal, risk-based design and development process shall be used to develop the aseptic process.

The design, development and risk management process shall:

- consider all core elements of an aseptic process (see [5.3](#));
- include a documented analysis of contamination risk.

6.1.2 The design output shall include:

- specification for each element of the aseptic process with verifiable performance criteria for which objective evidence can be generated during design qualification;
- process parameters for the aseptic process;
- materials and product handling processes (see [6.5](#)) including transfer systems (see [6.12](#)) disinfection, sterilization, depyrogenation and maintenance of sterility measures as applicable;
- the necessary manufacturing environment (see [6.6](#)) including clean room clothing systems (see [6.8.3](#)) and containment zones (see [6.12](#));
- risk controls identified in the risk analysis including critical control points (see [6.4](#));
- the basis for the development of the CCS (see [7.1](#));
- the strategy for design qualification using a risk-based approach for each process element.

NOTE 1 A risk-based approach assumes risks exist within a design. It identifies, assesses and ranks risks (in order of highest to lowest priority), implements strategies to preferably eliminate or at least reduce risk to an acceptable level (in order of risk priority) and adopts ongoing monitoring of risk to identify fluctuations in risk level.

NOTE 2 This is also known as a Quality-by-Design (QbD) approach. The approach proactively considers the impact of the process and equipment design on the quality attributes of product during the design phase.